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Review

Role of natural antioxidants and potential use of bergamot in treating rheumatoid arthritis

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ABSTRACT

The aim of the present review is to report about the effect of natural compounds, with proved antioxidant activity and mainly introduced with diet, on rheumatoid arthritis (RA). RA is a chronic, systemic inflammatory disorder leading to cartilage damage, bone erosions, joint destruction and impaired movement. The pathophysiology of RA includes reactive oxygen species (ROS) production, which is concomitant with inflammation and provokes a wide range of toxic reactions, like lipid peroxidation, inhibition of mitochondrial respiratory chain enzymes and modifications of membrane transport proteins. Since the development of effective therapeutic strategies to counteract RA is still in progress, the present review is intended to add more information about the possible role of natural antioxidant compounds in treating RA with a good balance between efficacy and toxicity. Natural products with proved anti-inflammatory and antioxidant actions such as (−)-epigallocatechin gallate, resveratrol, oleuropein, quercetin and the flavonoid fraction of bergamot juice are here being reviewed, with specific regard to their possible antioxidant therapeutic action against RA.

Contents

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1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by the activation of synovial tissue in the joint capsule, invasion of the cartilage and bone, with progressive joint dysfunction [1]. In RA, cartilage extracellular matrix components are degraded by matrix metalloproteinases (MMPs) as well as aggrecanases and large amounts of free radicals, such as reactive oxygen species (ROS), are produced by macrophages [2]. This disease occurs in approximately 1% of the adult population worldwide, often implying personal, family and financial consequences [3].

In the United States, RA and osteoarthritis (OA) affect more than 40 million people, with healthcare huge costs and the urgent need for more effective therapeutic treatments. In this regard, treatments targeting cytokines, like anti-tumor necrosis factor (TNF)-α antibodies, soluble TNF receptor, anti-interleukin (IL)-6 receptor antibody and IL-1 receptor antagonist, are currently used as a therapeutic approach for RA, in addition to anti-inflammatory agents and disease-modifying anti-rheumatic drugs, like inflimethotrexate. These treatments are not without risks though, especially in terms of costs and increased susceptibility of patients to infection. TNF-α blockers are very efficient, but, as the other side of the coin, one third of the RA patients are unresponsive or even exhibit adverse side effects [4].

Because of the limited success of disease-modifying anti-rheumatic drugs, the exploration of new anti-rheumatic agents with high efficacy and less toxicity is still in progress, and therapies relying on the use of natural substances have become increasingly marked. In this regard, an example is given by the anti-arthritic action of herbal extracts protecting cartilage destruction in arthritic diseases, as reported by Keisuke et al. [5].

Since ROS generation is concomitant with inflammation [6], leading to oxidation of proteins and lipids and further sustaining the inflammatory process, increasing interest has been addressed to the use of antioxidant compounds in treating RA. In particular, compounds extracted from plants, such as flavonoids, terpenes, quinones, catechins, alkaloids, anthocyanins and anthoxanthins, all of which are known to elicit antioxidant effects, can modulate the expression of pro-inflammatory signals and exhibit potential against arthritis [7]. The use of natural antioxidants is promising, though requiring more extensive investigations in preclinical and clinical procedures to prove their usefulness and, as stated by Khanna et al. [7], may serve as a gold mine for treatment of RA.

In the present review, the effect of antioxidant natural substances and their possible use against RA have been considered, with specific regard to (−)-epigallocatechin gallate, resveratrol, oleuropein, quercetin and the flavonoid fraction of bergamot juice.

2. Pathophysiology of rheumatoid arthritis and therapeutic strategies

The understanding of RA pathogenesis and, hence, the development of opportune therapeutic strategies include the use of animal models, like rat or mouse models of autoimmune erosive arthritis [1]. In this regard, Adipue et al. [8] discovered that mice in their breeding colony spontaneously developed inflamed joints reminiscent of RA and may, therefore, provide a new model to examine pathogenic mechanisms and test new treatments for this human inflammatory disease.

Type II collagen-induced arthritis (CIA) in the mouse is recognized as a useful model of RA, being cell and humoral immunity characteristics hallmarks of the pathogenesis common to human RA [9], like recruitment and activation of neutrophils, macrophages and lymphocytes in joint tissues and the formation of the pannus. RA finally implies the destruction of affected joints. The inflamed synovium consists of diverse cell populations, including B cells, T cells, macrophages and synovial fibroblasts (SF), leading to abnormal immune phenomena in the joint, chronic inflammation and synovial hyperplasia and contributing to the progression of the disease.

Synovial fibroblasts are responsible for the destruction of the joint, by secreting matrix degrading enzymes, and maintain inflammation by inducing pro-inflammatory cytokines production. Macrophages are also involved in TNF-α and IL-1 release, when in contact with T cells in the inflamed synovium. Hence, the role of cytokines, along with other inflammatory mediators in RA pathogenesis, has been ascertained and is a major issue under debate to develop effective targeted therapies against RA [10].

Cytokines activate the nuclear factor (NF)-κB, the p38 stress activated MAP kinases (MAPK) and PI-3 kinase [11,12], contributing to the maintenance of a chronical pro-inflammatory cytokine milieu in the synovium and triggering catabolic enzymes production. Monoclonal antibodies such as infliximab and adalimumab, as well as eternacept that inhibit TNF-α, have been used successfully in the treatment of RA [13]. On the other hand, targeting MAPK pathways, including the extracellular signal-regulated kinase (ERK), c-Jun amino terminal kinase (JNK) and p38 [14] to treat RA may be not a fully effective therapeutic tool, as all inhibitors of p38 MAPK do affect each isoform.

The TNF family member Fas ligand (FasL) has been also reported to trigger apoptosis in fibroblast-like synoviocytes (FLS) of arthritic joints by binding to its receptor Fas. Therefore, it is suggested as a promising candidate for targeting the hyperplastic synovial tissue. This is the question underscored by Calmon-Hamaty et al. [15].

Since it has been demonstrated that in RA some kinases participate in the generation of pathogenic signaling cascades, the pharmacological inhibition of kinases may be also considered as an effective therapeutic strategy against RA. Oral inhibitors of JAKs, Syk, PI3Ks, MAPKs and Btk are actually under development or in clinical trials in patients with RA, as pointed out by Chakravarty et al. [16].

Moreover, Toll-like receptors (TLRs) are also involved in RA pathogenesis, as their activation induces the expression of many inflammatory cytokines, chemokines and co-stimulatory molecules from antigen presenting cells. Therefore, a deregulation in the activation of TLRs can modulate the development of autoimmune diseases. In RA, TLR ligands have been detected in the joint of the patients [17].

The discovery of key intracellular pathways, particularly kinases which modulate cytokines function and immune cell receptors implicated in RA pathogenesis, is promising for drug development. Thus, a range of kinase inhibitors has effectively entered clinical trials, as recently reported by Meier and McInnes [18].

Pain and swelling reduction, delay of disease progression and improvement quality of life in RA patients are also goals of therapeutic intervention against RA. For pain control and swelling, treatment includes analgesics, such as acetaminophen and opioids, non steroidal anti-inflammatory drugs (NSAIDs), and intra-articular therapies, such as glucocorticoids. In addition, disease modifying anti-rheumatic drugs (DMARDs) are used to modify the clinical and radiological course of RA. Examples are given by methotrexate (MTX), sulfasalazine, leflunomide, hydroxychloroquine and newer therapies, such as TNF-α therapy (etanercept, infliximab and adalimumab), anti-CD20 therapy (rituximab) and abatacept. Nevertheless, these agents are associated with several side effects [7].

Another approach to the treatment of RA is aimed to counteract ROS production occurring in RA. Free radicals are chemical species possessing an unpaired electron. The synovial fluid and peripheral blood of RA patients have high levels of ROS and

ROS-generated molecules, including superoxide, peroxide, hydroxyl radicals and reactive nitrogen species (RNS), like peroxynitrite [2,19].

In vivo experiments carried out in Freund's complete adjuvant (FCA) – induced rats showed that neutrophils, macrophages and dendritic cells generate ROS in large amounts in response to inflammation [20]. The activated O_2 intermediates, together with secondarily formed radicals like hydroxyl radicals, are in fact able to destroy membrane lipids, proteins, DNA and cartilage [21]. O_2^-, the 1-electron reduction product of oxygen, perpetuates the chronic inflammatory state associated with RA and a superoxide dismutase mimetic (SODm), like M40403, has been demonstrated to exert a beneficial effect in the collagen-induced arthritis (CIA) model [22].

With regard to clinical studies, increased lipid peroxidation and malondialehyde (MDA) levels and decreased enzymatic and non-enzymatic antioxidants are found in RA patients, but glutathione-peroxidase (GSH-peroxidase) and superoxide dismutase (SOD) activities are lower, suggesting that an increase in oxidative stress and a low antioxidant status occur in RA patients [23]. Therefore oxidant stress plays a critical role in the pathogenesis of RA disease.

Defense mechanisms against oxidative stress, SOD, GSH-peroxidase, catalase (CAT) and glutathione S-transferase (GST), compensate for the toxicity resulting from ROS. ROS produced by severe or chronic inflammation may exceed the capability of the corresponding anti-oxidant enzymes, which seems to cause imbalance in the redox state [24]. An excess in ROS production disrupts this redox balance and amplifies inflammatory responses *via* NF-κB, which, as said above, is a central regulator of cellular inflammatory response, as it controls many of the genes involved in inflammation [25,26].

ROS also have direct effects as they oxidize and degrade the major components of cartilage and bone, including collagen and hyaluronic acid (HA) [2]. The degradation of hyaluronic acid (HA) is, at least in part, the result of fragmentation by hydroxyl radical [2,27] and seems to be responsible for the decreased viscosity of joint fluid observed in RA patients. The positive feedback resulting from the accumulation of oxidized products could further exacerbate the cartilage and bone erosion, and lead to joint destruction. Therefore, protection of the joint components from the direct degradation by ROS represents another potential target of RA therapy.

What is more, oxidative stress may participate in the etiology of RA through direct interaction with DNA. An example is given by 8-OHdG, produced by the oxidation of guanine bases of DNA [28], whose levels are elevated in RA patients [29]. It is highly mutagenic since it pairs with adenine as well as cytosine, provoking transversion mutations during DNA replication. Therefore ROS, by inducing somatic mutations, alter protein function and/or immunogenicity, contributing to further activate the immune system [30].

3. Natural antioxidants and rheumatoid arthritis

Since ROS production is a hallmark for RA, one therapeutic approach to treat RA is to remove ROS. For this reason, the use of antioxidants to treat RA has been considered by many researchers [31], with specific regard to natural compounds with proven antioxidant effect [7,32,33].

Some studies have provided evidence of a link between dietary antioxidant intake and the likelihood of developing inflammatory arthritis, albeit the pathways underlying antioxidant compounds action are not completely understood. Nevertheless, the potential therapeutic role of dietary antioxidants in inflammatory arthritis is an issue rising much interest [34]. Amongst natural antioxidants, flavonoids and in particular the flavonoid fraction of bergamot juice, are worthy of note and are being considered in this review for their possible benefit in treating RA.

3.1. Flavonoids

Flavonoids are organic molecules, secondary metabolites of plant cells, including many edible plants, where they exert a protective action against ultraviolet radiation and oxidative stress [35]. They represent a notable part of human supply and several studies have shown that high regular intake of some phenolic compounds in the diet provides a preventive action against several human diseases, such as cardiovascular pathologies, atherosclerosis, osteoporosis, allergies, diabetes, neurodegenerative diseases and cancer [3]. Although the mechanisms by which these natural compounds exert their benefits are not completely clarified, anti-inflammatory effects of flavonoids have been attributed primarily to their antioxidant activity, because they are known to scavenge and prevent the formation of ROS and RNS [36]. Moreover, flavonoids could influence cellular function by direct interaction with receptors, modulation of intracellular signaling and inhibit the activities of many inflammatory proteins such as NF-κB and the expression of genes associated in chronic inflammatory disease [37].

The main sources of flavonoids are the daily intake of tea and *Citrus* fruits and juices. Amongst the *Citrus*, bergamot (juice or essential oil) has been rising the interest of many researchers in the recent years, due to its recognized beneficial properties, so that it is now considered a new challenge in the field of therapeutic strategies development, namely against inflammatory diseases.

3.1.1. Bergamot

Citrus bergamia Risso et Poiteau (Rutaceae) is a fruit typical of a limited coastal area of the province of Reggio Calabria, Italy, where both climate and environmental conditions are favorable for its cultivation. Bergamot fruit is mainly used to extract the essential oil (BEO) obtained from the peel, much employed in perfumery, cosmetic, pharmaceutical and food industries [38]. BEO, obtained by cold pressing of the epicarp and, in part, of the mesocarp of the fresh fruit of bergamot, comprises a volatile fraction (93–96% of total) containing both monoterpene and sesquiterpene hydrocarbons (such as limonene, c-terpinene, a- and β-pinene, β-myrcene, sabinene and β-bisabolene) and oxygenated derivatives (such as linalool, linalyl acetate, neral, geranial, neryl acetate and geranyl acetate), and a non volatile fraction (4–7% of total) characterized by coumarins and furocoumarins, such as bergapten (5-methoxypsoralen) [38,39].

In Italian folk medicine BEO has been long used as antiseptic and to facilitate wound healing due its antifungal [40] and antimicrobial [41] properties.

The use of this essential oil has been considered in aromatherapy [38], for the relief of pain and anxiety/depression symptoms and has been shown to modulate the release of neurotransmitters in discrete brain regions under both basal and pathological conditions [42]. In this latter regard, the intraperitoneal administration of BEO has been reported to significantly increase the extracellular levels of the inhibitory amino acid neurotransmitter gamma-aminobutyric acid (GABA) in rat hippocampus [42]. This effect on the GABAergic system may account for anxiolytic related behavioral effects, comparable to benzodiazepine anxiolytic drugs, which are known to act by increasing GABA function in the brain [43]. Moreover, *in vitro* experiments suggested the potential neuroprotective activity of BEO [44].

In the cardiovascular field, it has been shown that the non-volatile fraction of BEO reduced the neointima proliferation in an experimental model of rat angioplasty, inhibiting both free

radical production and lectin-like oxyLDL receptor-1 (LOX-1) expression [45]. Moreover, BEO induces vasorelaxation in the mouse aorta by activating K^+ channels and inhibiting Ca^{2+} influx [46].

Finally, the biological properties of the BEO have been explored even in experimental oncology. Ursino et al. were the first to report the antiproliferative activity of BEO in the SH-SY5Y neuroblastoma cells, suggesting a potential role against cancer in a context of a multitarget pharmacological strategy [47]. Very recently they have added new findings on the pharmaco-toxicological profile of BEO, revealing the activation of multiple pathways leading to both necrotic and apoptotic SH-SY5Y cell death [48]. Finally, to improve the water solubility of the phytocomplex, they formulated BEO liposomes, thus increasing the *in vitro* anticancer activity of BEO and its fractions [49].

Despite bergamot juice (BJ), obtained from the endocarp of the fruit, is often considered a secondary product of the essential oil industry, it has been actually recognized as a source of beneficial effects. In this regard, BJ chronic administration has been shown to prevent the diet-induced hyperlipidemia in rats [50]. Moreover, a significant reduction of serum cholesterol, triglycerides and glycemia has been described in patients suffering from metabolic syndrome and treated with bergamot-derived polyphenolic fraction [51].

BJ has been also demonstrated to reduce the proliferation of several tumor cell lines such as SH-SY5Y, PC12, PC3 and MDA-MB-231 cells showing the strongest growth rate inhibition in SH-SY5Y cells. In this cell line, the antiproliferative effect of BJ was not due to a cytotoxic action, but to a marked reduction of cell adhesiveness together with a block of the cell cycle in the G1-phase, caused by a reduced expression of cyclin D1 [52]. In this regards, the cell cycle modulation by *Citrus* flavonoids exhibiting antiproliferative effects has been already described [53]. Moreover, the ability of BJ to interfere with the cytoskeleton reorganization and the actin remodeling impair the migratory machinery and may be responsible for the anti-metastatic effect of BJ observed in a spontaneous metastatic neuroblastoma SCID mouse model [54]. Interestingly, the *in vitro* antiproliferative and anti-mestastatic effects occur without cytotoxic effects neither in tumor nor in normal cells. Moreover, no apparent sign of systemic toxicities was detected when *in vivo* experiments were performed, suggesting thus a potential role of BJ in oncologic field. More recently, it has been demonstrated that the antiproliferative properties of BJ are referable to its flavonoids, since the flavonoid fraction of BJ (BJe) reduced the growth rate of colon cancer cells [55].

Another set of experiments, carried out by Navarra and co-workers, demonstrated that BJe is able to significantly reduce both transcription profile and protein levels of pro-inflammatory cytokines in LPS-stimulated THP-1 monocytes, a human leukemia monocytic cell line widely used as a model to study the inflammatory cell response [56]. In particular, the authors reported that BJe modulates NF-κB pathway, likely *via* SIRT1 activation, demonstrating an *in vitro* anti-inflammatory activity of flavonoid fraction from BJ. Thus, it is reasonable to propose that BJe may represents a novel pharmacological strategy to prevent inflammatory responses. Finally, very recently the treatment with BJe has been demonstrated to exert both antioxidant and anti-inflammatory activity in an experimental model of inflammatory bowel disease, suggesting that BJe could represent a target for therapeutic intervention in autoimmune/inflammatory disorders, such as colitis [57].

3.1.2. Other flavonoids

Many studies contributed to verify the antioxidant effect of other flavonoids and their potential use against inflammatory diseases, like RA. Luteolin, a common flavonoid found in plants such as *Apium graveolens* L. var. dulce, *Petroselium crispum*, and *Capsicum annuum* L. var. grossum, possesses antioxidant and anticancer actions and has been considered for its protective effect against oxidative stress-induced inflammation and cell damage [58]. In this regard, Impellizzeri et al. [59] interestingly proposed the use of a combined treatment with the endocannabinoid PEA and the flavonoid luteolin to counteract the inflammatory process associated with RA in a mouse model. These authors showed that a co-ultramicronized PEA + luteolin formulation (PEA-LUT) is protective in a model of collagen-induced arthritis. Furthermore, they demonstrated that the formation of highly reactive nitrogen derivatives and chondrocyte lipid peroxidation, responsible for cartilage oxidation/degradation [1], are significantly reduced by PEA-LUT formulation and that the effect of PEA alone in reducing the inflammatory response is potentiated by the combination with the flavonoid luteolin.

Quercetin (QU) (3,3′,4′,5,7-pentahydroxy flavone) is a natural flavonoid, found in herbs, vegetables and fruits (broccoli, tea, onions and apples), exhibiting different biological activities. It has been shown to prevent or reduce inflammatory reactions by regulating NF-κB activation and inhibiting the transcription of joint synovial inflammatory factors. Nevertheless, QU has been reported to inhibit the activity of VEGF, bFGF, MMP-2 and other cytokines, inhibit angiogenesis and synovial pannus formation, thus suggesting that QU, playing a role in counteracting RA inflammation, may be reasonably proposed as an adjuvant drug for RA treatment [60].

Genistein, the major active compound from soybean, has attracted the attention of many researchers, due to its proven antioxidant, anti-inflammatory, antiangiogenesis, immunomodulatory, pain relief and joint protection properties. Li et al. [61], on the basis of these properties assayed on both *in vitro* and *in vivo* models, propose genistein as a promising agent for RA treatment. Genistein possess strong cytoprotective activity, inhibiting cytokine-mediated toxicity, breast cancer and promoting chemotherapeutic efficacy. Genistein's mechanisms of action include inhibition of tyrosine kinases, activation of PPAR-gamma and binding of estrogen receptors [35].

3.2. Other natural antioxidant compounds

3.2.1. Oleuropein

Olive oil with its unique characteristics is an ingredient comprised in the traditional Mediterranean diet, whose beneficial effects are recognized [62]. The major constituent of the leaves and unprocessed olive drupes of *Olea europaea* is oleuropein and the majority of polyphenols found in olive oil derives from its hydrolysis. Oleuropein elicits high antioxidant activity *in vitro*, comparable to that of a hydrosoluble analog of tocopherol [63], scavenges superoxide anions and hydroxyl radicals and inhibits the respiratory burst of neutrophils and hypochlorous acid-derived radicals [64].

Impellizzeri et al. [65] have proposed a mouse model of arthritis, induced by injection of collagen type II (CII), to study the inflammatory response and its possible amelioration under oleuropein treatment. These authors observed that oleuropein aglycone, a hydrolysis product obtained from oleuropein by the action of beta-glucosidase [66], ameliorates arthritis progression by reducing the activation of the nuclear enzyme poly(ADP-ribosyl) polymerase (PARP) involved in inflammation [67], with a decrease in PAR expression in the inflamed joint. It is likely that oleuropein aglycone, given at the onset of the disease, may reduce paw swelling and the histological damage due to RA. Other authors support these data, with specific regard to the reduction of ROS

levels, demonstrating the antioxidant effect of olive oil phenols and their beneficial effects against inflammation [68].

3.2.2. Epigallocatechin-3-gallate

Green tea (*Camellia sinensis*) is one of the most commonly consumed beverages in the world and is a rich source of polyphenols known as catechins (30–36% of dry weight) including epigallocatechin-3-gallate (EGCG), which constitutes up to 63% of total catechins [69]. A cup of green tea typically provides 60–125 mg catechins, including EGCG, which has been shown to be 25–100 times more potent than vitamins C and E in terms of antioxidant activity [70]. In the past EGCG has been extensively evaluated for its potential anti-rheumatic activity using *in vitro* and *in vivo* arthritis models, providing evidences to consider this compound a candidate for therapy against RA.

EGCG suppresses IL-1-induced glycosaminoglycan release from cartilage by blocking NF-κB activity in chondrocytes and inhibits those processes responsible for cartilage degradation, like IL-1-stimulated inducible nitric oxide synthase (iNOS). Both *in vitro* and *in vivo* studies suggest that EGCG could reduce synovial hyperplasia, cartilage degradation and bone resorption by modulating multiple targets in joints [71]. Nevertheless, preclinical studies are still needed to better support the efficacy of its antioxidant power in treating patients with joint diseases [72].

3.2.3. Resveratrol

Resveratrol (*Vitis vinifera*, ortrans-3,5,40-trihydroxystibene) is a constituent of the roots of white hellebore (*Veratrum grandiflorum* O. Loes), but it is also found in plants like grapes, berries and peanuts [73]. Some studies indicate that this stilbene could be involved in the prevention and treatment of arthritis by suppressing ROS production, IL-1 synthesis, p53-induced apoptosis and prostaglandin E2 synthesis [74]. In particular, it has been shown that intra-articular resveratrol treatment reduced cartilage loss in rabbit arthritis models and RA-related pannus formation, useful in treating RA. It has been already demonstrated [7] that resveratrol can suppress NF-κB activation. This issue has been more recently further investigated [75], in an attempt to unravel the mechanisms by which resveratrol elicits antiapoptotic and anti-inflammatory effects. In this regard, the authors described a modulation of *in vitro* tumor promotion by resveratrol, acting *via* inhibition of the NF-κB signaling pathway. Moreover, *in vivo* investigations further confirmed the anti-inflammatory properties of resveratrol, showing that it reduces TNFα, IL-1β and IL-6 levels in a rat model of Hepatocellular carcinoma (HCC) [76]. Hence, the anti-inflammatory effect of resveratrol induced many researchers to verify its possible beneficial actions in rheumatoid arthritis (RA). In particular, Tian et al. [77] demonstrated that resveratrol attenuates TNF-α-induced production of IL-1β and matrix metalloproteinase (MMP-3) *via* inhibition of PI3K-Akt signaling pathway in rheumatoid arthritis fibroblast-like synoviocytes (FLS).

In addition to *in vitro* studies, clearly showing the beneficial effects of resveratrol, clinical trials are certainly needed to confirm its efficacy in the prevention and treatment of arthritis, taking into account that, despite these anti-inflammatory and antioxidant activities, resveratrol oral consumption and tissue bioavailability are problematic [7,35].

3.2.4. Curcumin

Curcumin (diferuloylmethane), an orange-yellow component of turmeric or curry powder, is a polyphenol natural product isolated from the rhizome of the plant *Curcuma longa*. For centuries, curcumin has been used in medicinal preparations or used as a food-coloring agent and its recognized cytoprotective effects may be attributed to its potent antioxidant activity [35]. Recently, *in vitro* and *in vivo* studies indicated that curcumin exhibits anticancer, antiviral, antiarthritic, anti-amyloid, antioxidant and anti-inflammatory properties. On this basis it has received considerable interest as a potential therapeutic agent for the prevention and/or treatment of various malignant diseases, arthritis, allergies, Alzheimer's disease and other inflammatory illnesses. Curcumin mitigates inflammatory responses by inhibiting cyclooxygenase-2 (COX-2), lipoxygenase, NFκB, inducible nitric oxide synthase, and NO production [78,79]. The anti-inflammatory effects of curcumin are partly mediated *via* inhibition of the transcription factor NF-kB and activator protein (AP)-1, inhibition of pro-inflammatory cytokines expression in many cell types [35]. Other targets with which curcumin interacts include phosphorylase-3 kinase, xanthine oxidase, *N*-aminopeptidase, amyloid protein, autophosphorylation activated protein kinase, DNA polymerase, glutathione, albumin, tubulin, topoisomerase II and toll-like receptor (TLR)4. Because most chronic diseases are mediated through dysregulated inflammation, curcumin has potential use in the prevention of these diseases. Enhanced bioavailability of curcumin in the near future makes this natural product promising for the treatment of human diseases [80,81]. However more clinical trials are needed to fully realize its potential.

4. Conclusion

Various dietary components like natural antioxidant and, namely, flavonoids could modulate predisposition to chronic inflammatory conditions and may have a role in their therapy. These components act through a variety of mechanisms including the reduction of both inflammatory mediators production, *via* cell signaling and gene expression modulation, and damaging oxidants production. However, really strong evidence of benefit to human health through anti-inflammatory actions is lacking for most of these dietary components. Thus, further studies on the efficacy in humans and on understanding the involved mechanisms of action are required [81].

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